

Cancer proteomics in India

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Enormous efforts have gone into understanding the mechanism behind cancer pathogenesis using cell and molecular biology approaches, cell lines and animal models. Several investigators from India are actively contributing to the understanding of oncogenic processes using these approaches.

Cancer proteomics in India started with work on gliomas – the most common and aggressive adult primary tumours of the brain and oral cancers, which form a large part of the total head and neck cancer burden in the country. This multi-institutional programme by the Council of Scientific and Industrial Research included gene expression analysis at the transcript level.

The first publication on cancer proteomics from India was on gliomas in 2005¹. In the last decade, over 50 other publications have appeared on oral cancers, gastro-intestinal tract cancers and some others.

Analysis methods

Early cancer proteomics efforts relied upon available technology and infrastructure – the 2DE-MS approach and its advanced variation 2D-DIGE^{1, 2, 3}. These approaches offered limited proteome depth leading to application of alternative strategies that enabled deeper protein analysis. These included shot-gun proteomics through the liquid chromatography–mass spectrometry (LC-MS or MS) approach for the first time in oesophageal cancers⁴ and gliomas⁵ and generated larger and deeper protein datasets.

Scientists prefer the antibody based approaches (ELISAs, tissue microarrays or TMAs) for confirmation and validation of markers. TMAs have been used for the validation of candidate proteins for oesophageal tumours⁶ and glioblastomas⁷ and in a variety of cancers in the Human Tissue Proteome Map⁹.

Direct profiling has remained a major technical challenge for body fluid proteomics. Indian researchers have used tumour cell secretome analysis as an important alternative^{4, 8, 9, 10}. Exosomes, which carry circulatory nucleic acids and proteins, are also emerging as an attractive choice for the analysis of circulatory biomarkers.

Indian studies

Indian proteomics studies have largely remained at the first stage of biomarker development – the discovery stage – though recently there have been some efforts to translate discovery leads to clinical applications.

A glioma research group has used clinical tissues, plasma samples and cell lines to get large data using gel-based and gel-free proteomics approaches. The data is extensively annotated for biology and tumour related processes^{5, 8, 9, 11, 12}. Candidate proteins from this dataset are being evaluated for molecular typing of tumours, post-treatment surveillance and therapeutic applications¹³.

Indian scientists have also conducted extensive gene expression studies on gliomas and extrapolated them to the protein level. These studies have identified potential markers, undertaken molecular typing of glioma grades and analysed candidate regulatory molecules using cell lines^{14, 15, 16, 17}. Some groups have used a different approach to screen gliomas for autoantibodies on human protein arrays. Their investigations are targeted towards identifying proteins specific to the grade, aggressiveness and invasiveness of these tumours^{18, 19}.

Oral cancers form a major proportion of the cancer burden in the country. Using 2DE-MS based investigations and quantitative LC-MS/MS methods with oral cancer tissues, differentially expressed proteins have been identified^{2, 20}. Candidate markers are being evaluated in different cohorts²¹ and for more defined clinical queries. Some of them are also being assessed to distinguish histologically normal surgical margins for tumour areas²². Investigators have also identified predictive markers in pre-malignant lesions²³. Specific proteins eliciting an autoantibody response in oral cancer patients have been identified using immunoproteomics²⁴. Secretomes of cell lines from head and neck cancers have been analysed¹¹. Cell line models chronically exposed to tobacco extracts or smoke have been developed to create risk prediction markers for tobacco induced oral cancers, and differentially altered proteins have been identified. Studies are on to distinguish dysplastic leukoplakia, early stage and late stage oral tumours using salivary proteins.

Oesophageal squamous cell carcinoma and gastric cancer are significantly common malignancies in Asia meriting many investigations by Indian groups^{4, 6, 25, 26}. Quantitative gene expression studies at mRNA and protein level have identified many novel proteins. Using phosphoproteomics and functional assays, signalling molecules such as cell surface receptors have been identified. A key molecule possibly involved in tumour development has been identified and validated in clinical specimens.

India falls under the endemic region for gall bladder cancer and efforts are on to understand the disease at the molecular level through proteomic and phosphoproteomic profiling of gall bladder

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cell lines. Some other cancers studied with proteomic approaches are urinary bladder cancer²⁷ and ovarian tumours²⁸.

On the way to translation

Some of the leads on gliomas are showing translational promises^{14, 15, 16, 17}. Glioma proteomics data is well on its ways for use in tumour typing and post treatment surveillance¹³.

Autoantibody response to specific tumour antigens have shown merit in oral cancer prognosis²⁹. Indian scientists are also exploring the potential utility of candidate salivary proteins to define dysplastic leukoplakia. A biomarker-based, ultrasensitive chip consisting of arrayed immunosensors is currently being examined as a point-of-care screening device.

A recent report³⁰ describes analysis of predicting treatment response in patients with head and neck cancers – a step towards personal medicine. Proteomics-based clinical applications backed by state-of-the-art experimental and analytical methodologies are thus yielding some encouraging results for Indian proteomics researchers. However, these efforts need intensification. Specific clinical questions – big and small – have to be asked for the benefit of the diverse Indian patient population. Appropriate patient cohorts and accessibility of large number of clinical specimens are going to be a key requirement.

In recent years, many medical centres have set up big and small sample repositories. The bigger challenges to India's health care system, however, are lack of physical samples, scarce clinical annotation and poor follow-up patient data. The country's medical record informatics system needs a big overhaul with long term support from both public and private sector so as to facilitate more effective translation in this multi-disciplinary, multi-centric field.

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